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14. ABSTRACT
It is estimated that 10% to 20% of warfighters who have served in Iraq and Afghanistan have PTSD 1-4. An important limitation of these estimates is the reliance on self-report screening measures and clinical interviews to make the diagnosis of PTSD. These methods are subject to a number of biases, including underreporting of PTSD symptoms because of stigma of mental illness and concerns about adverse effects on careers, and exaggeration of symptoms in those seeking compensation for service- connected disability. Development of biomarkers of PTSD is critical for DOD and VA as objective indicators of PTSD for use in post-deployment medical screening, treatment selection, treatment outcome monitoring, disability evaluations, and for informing novel targets for treatment development.

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INTRODUCTION:

It is estimated that 10% to 20% of warfighters who have served in Iraq and Afghanistan have PTSD [1-4]. An important limitation of these estimates is the reliance on self-report screening measures and clinical interviews to make the diagnosis of PTSD. These methods are subject to a number of biases, including underreporting of PTSD symptoms because of stigma of mental illness and concerns about adverse effects on careers, and exaggeration of symptoms in those seeking compensation for service- connected disability[5]. Development of biomarkers of PTSD is critical for DOD and VA as objective indicators of PTSD for use in post-deployment medical screening, treatment selection, treatment outcome monitoring, disability evaluations, and for informing novel targets for treatment development. Additionally, biomarkers hold great potential for explaining and mitigating the associations between war zone-related PTSD and physical health problems, including cardiovascular and metabolic disorders [6-10]. In order to address this critical gap we will perform a pilot study to determine feasibility for larger scale biomarker identification and biomarker informed intervention studies by carefully examining 200 OIF/OEF warfighters through an extensive biological protocol. The first phase will pilot the integration of methods across five leading research laboratories and identify the most promising biomarkers in preparation for larger scale studies. Given the sample size for the pilot and large number of biomarkers of interest, we will specify a limited set of biomarkers for hypothesis testing. It is predicted that compared with controls the PTSD group will have smaller dentate/CA3 hippocampal subfield volumes, lower ambient cortisol levels, and greater cortisol suppression following dexamethasone administration. It is also predicted that lower neuropeptide Y levels will be associated with smaller Dentate/CA3 volumes, and that APO E4 polymorphisms will be associated with smaller Dentate/CA3 volumes.

BODY:

The Biomarkers for PTSD study is in the implementation phase. In year 2 of the grant we accomplished several milestones and goals. These accomplishments are detailed below:

1. IRB

The continuation application for this study was reviewed by all sites (NYU, Bronx VA, Mount Sinai and UCSF) and approved by these collaborating sites and the DOD IRB (HARPO).

2. Communication Strategies

Weekly meetings, through teleconference calls, took place between PIs at each site (Bronx VAMC, UCSF, Mt Sinai, and NYU). Meetings focused on issues related to calibration of clinical interviewing across sites, strategies for maintaining a high rate of subject recruitment and enrollment, strategies for maximizing participation in Visits 2-4 and ensuring that participants moved through all stages of the study quickly and efficiently (in order to avoid attrition).

Core PIs participated via Web-Ex in an internal quarterly meeting on May 3rd & May 8th 2012 presenting preliminary findings from each core.

PIs participated in the Systems of Biology quarterly meetings and provided preliminary data on demographics of the recruited sample, data from diagnostic clinical evaluations, self reports and neurocognitive data. Preliminary biomarkers data on neuroimaging, genetics, endocrine and metabolic biomarkers were also presented during the May 14, 2012 meeting.

3. Recruitment of Subjects

According to the Statement of Work, the goal of this grant is to enroll 200 OIF/OEF male veterans. In year 2 of the grant 142 participants meeting all study criteria were recruited and enrolled in the study. Of those 60 participants were PTSD positive. To date 110 participants successfully completed all study procedures.

4. Data Management

All Clinical Assessment data from the baseline interview, self-report and neurocognitive measures for all study participants were completed and entered as digital data directly into the study secure SQL database server. Data from all cores is also shared with NYU and saved into a single database. Study data was cleaned and scored by the biostatistician and shared with all PIs and investigators in preparation for the internal PI quarterly meeting presentations.

5. Acquisition of Study procedures

All study procedures including blood draw procedures and MRI imaging are completely operational.

Please see table below for details on total study procedures completed to date:

Biomarkers For PTSD	
BCI Evaluation	
Clinical Assessment	269
Eligible by Evaluation	142
PTSD+	60
PTSD-	82
Cognitive Testing	
Completed	128
PTSD+	53
PTSD-	75
Self-Report Questionnaire	
Completed	131
PTSD+	55
PTSD-	76
Visit 2 Blood Draw (1)	
Completed	125
PTSD+	56
PTSD-	69
Visit 3 Blood Draw (2)	
Completed	122
PTSD+	56
PTSD-	66
MRI	
Completed	120
PTSD+	48
PTSD-	72

6. Shipment of Material to cores

Shipments of Blood samples were transferred to all collaborating sites, Walter Reed Army Institute of Research (WRAIR): Mouse Models of PTSD (Principal Investigator Dr. Jett), and Institute for Systems Biology (ISB): Genetics, Metabolomics (Principal Investigator Dr. Hood), Genetics Core at UCSF (PI: Dr. Steve Hamilton), and to the Metabolism Core at UCSF (PI: Dr. Owen Wolkowitz).

Data transfer from NYU to the imaging core at UCSF is running smoothly and Q & A procedures indicate high quality of data collection. All scans were processed through freeSurfer v5.1. Manual Hippocampal Subfield Marking on scans was completed on 70 subjects.

7. Data Sharing Agreements:

NYU and Bronx VA teams are working with Privacy Officers and Offices of Industrial Liaison/Technology Transfer (OIL) to execute Material Transfer Agreements (MTAs) with 6 specialized laboratories that will conduct analysis on assays for the metabolism core.

8. Preliminary Analysis

On May 14, 2012, the PI, Dr. Charles Marmar, presented preliminary study analysis at the Systems Biology meeting in Seattle. A summary of findings is listed below:

- There are a significant group differences in both current and past major depression
- There are significant group differences in alcohol abuse and dependence.
- There are significant differences between groups in Working Memory/attention using Digit Span, Spatial Addition (IQ is a trend toward significance)
- PTSD is associated with increased markers of allostatic load and with immune system dysregulation
- Metabolic dysregulation is directly associated with symptom severity
- BDNF concentrations are higher in PTSD positive subjects and are directly correlated with PTSD symptom severity
- Telomere shortening (indicative of cell aging) is directly associated with overall psychiatric symptom severity in PTSD positive subjects

KEY RESEARCH ACCOMPLISHMENTS:

- Obtained IRB continuation approvals across all sites and the DOD.
- Continued outreach efforts and networking with various veterans and community organizations. IRB approved recruitment material (brochures, flyers and advertisements) were distributed at job fairs, colleges, VA Medical Centers and veterans' organizations.
- Enrolled 142 OIF/OEF veterans and completed clinical assessments, self-report measures, and neurocognitive testing for these participants.
- Study team participated in weekly study meetings, quarterly internal meetings and Systems Biology meetings.
- Entered, cleaned, and scored all data into a centralized database and ran reports for data analysis.
- Completed biomarkers study procedures for eligible participants including blood draws, MRIs and urine collection.
- Completed a number of shipments of blood samples from JJPVAMC to UCSF (Metabolism & Genetic cores). Neuroimaging data was transferred successfully from NYU to UCSF.
- Drafted Material Transfer Agreements between JJPVAMC, NYU and outside specialized labs collaborating with the Metabolism Core at UCSF.

REPORTABLE OUTCOMES:

- The major development during the timeframe of this annual report for this project is that the implementation phase has been established and is well underway.
- Recruitment and data collection has begun and participants are completing all study procedures.
- Data is being transferred across sites and several specimen shipments were sent to the metabolism and genetics cores.
- Tasks to complete for the next annual report include: (1) Continue to recruit and enroll subjects for the study. (2) Run study participants through all procedures. (3) Continue data collection and data management. (4) Analyze demographic data for enrolled participants for the purpose of matching controls with PTSD positive participants. (5) Continue to process and ascertain biomarkers. (6) Test biomarkers for 50 cases/50 controls. (7)

Replicate the most promising biomarkers. (8) Continue to ship samples to UCSF, Drs. Marti Jett and Lee Hood for analysis. (9) Develop a publication policy.

CONCLUSION:

According to the Statement of Work, the goal of the implementation phase of this study is to:

1. Enroll and evaluate 200 OIF/OEF veterans (100 PTSD positive & 100 PTSD negative).
2. Complete all assessment measures for the enrolled participants
3. Complete Data entry for enrolled participants
4. Conduct biomarker acquisition procedures
5. Deliver Material to cores
6. Conduct preliminary analyses on sample

In year 2 of the project we exceeded the goals and milestones in the SOW by enrolling 70% of the required sample size, and meeting all the milestones for this project.

We will continue with preliminary data analysis on a sample size of 50 cases/50 controls. The most promising biomarkers will be replicated and compared with the animal model.

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